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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,971	11/26/2001	Markku Ahotupa	2630-113	8814

6449 7590 04/23/2004

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/991,971	AHOTUPA ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 19 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *None*.

   Claim(s) objected to: *None*.

   Claim(s) rejected: *1-6,17 and 18*.

   Claim(s) withdrawn from consideration: *7-16,19 and 20*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because:

The enablement rejection of Claims 1-6 and 17-18 stands rejected under 35 U.S.C. 112, first paragraph.

Applicants' arguments filed 3/19/04 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present claims are directed to a method for inhibiting the overactivity of phagocytes or lymphocytes in an individual by administering an effective amount of a lignan of the specific formula. (2) The present claims are not directed to the treatment of any diseases. (3) The specification demonstrates the in vitro activity of the claimed lignans. (4) A skilled artisan has reasonable expectation of success between in vitro and in vivo effects. Dandona et al, of record, demonstrates that the drug carvedilol has antioxidative effects in humans in vivo. Devaraj et al., of record, demonstrates that alpha tocopherol (vitamin E) has anti-oxidative properties in humans in vivo. The specification Table I shows that both hydroxymatairesinol and matairesinol have effect on neutrophils and oxidative burst and myeloperoxidase activity. Example 2 and Figures 2 and 3 show that hydroxymatairesinol, matairesinol and enterolactone all have an effect on T lymphocytes. (5) Pool-Zobel et al (of record) does not disclose any in vivo experiment. Both of the Figures 4 and 5 of Pool-Zobel et al relates to in vitro experimentation. The cell used in the Pool-Zobel et al are entirely different from the phagocytes and lymphocytes which are affected according to the present invention.

In response, the claims encompass a method of inhibiting a genus of overactivity of phagocytes or lymphocytes in an individual by administering "a mixture of hydroxymaairesinol and matairesinol" if the phagocytes are neutrophils, "a mixture of enterolactone and hydroxymatairesinol" if the phagocytes are myeloid origin, a mixture of hydroxymatairesinol, matairesinol, and enterolactone" if the lymphocytes are T lymphocytes. The specification discloses only a method of inhibiting oxidative burst and myeloperoxidase by administering individual lignan hydroxymatairesinol or matairesinol to neutrophils in vitro. The specification further discloses pretreating Jurkat T cells with either hydroxymatairesinol, enterolactone or matairesinol increases Fas mediated apoptosis (Fig 2) by increases Fas receptor expression on T cell in vitro (Fig 3). The specification also discloses enterolactone or matairesinol treatment inhibits LPS mediated TNF alpha production by monocytes in vitro. However, the specification fails to teach a "mixture" of lignans for the claimed method of inhibiting overactivity of phagocytes or lymphocytes. Further, there is a lack of in vivo working example demonstrating that each lignan has inhibitory activity in vivo. In fact, the specification teaches pretreating Jurkat T cells with either hydroxymatairesinol, or enterolactone or matairesinol increases Fas mediated apoptosis (Fig 2) and increases Fas receptor expression on T cell in vitro (Fig 3), just the oposite of inhibiting the "overactivity of lymphocytes". The specification discloses on page 4 paragraph 19 that a further object is to inhibit the overactivity of T lymphocytes by inducing their self-destroying activity, and thereby lower the risk, prevent or treat diseases or conditions due to this mechanism. The specification on page 6 discloses the conditions which can be treated or prevented by administering hydroxymatairesinol, matairesinol or enterolactone are allergic condtions, autoimmune diseases such as rheumathroid arthritis, inflammatory bowel disease, asthma, psoriasis, type I and type II diabetes, rejection due to tissue transplant, atherosclerosis, and multiple sclerosis, Alzheimer's disease, HIV, and AIDS. Given the indefinite numer of diseases, the lack of in vivo working examples, different lignan have different effects on different cell type, it is unpredictable which overactivity of phagocytes or lymphocytes that the claimed method can inhibit in vivo. The specifcation does not teach how to extrapolate in vitro data to in vivo method of inhibiting which overactivity of phagocytes or lymphocytes associated with which particular condition. Until a specific overactivity of phagocytes or lymphocytes associated with a particular condition that the claimed method has been demonstrated in vivo, the specification as filed merely invites one skill in the art for further experimentation to arrive at the claimed invention.

In response to Dandona et al and the Devaraj et al references, it is noted that the drug carvedilol and tocopherol (vitamin E) have completely different structures than the lignans hydroxymatairesinol, matairesinol and enterolactone required by the claimed method. In short, the references are irrelevant to the claimed invention.

In response to Pool-Zobel et al does not disclose any in vivo experiment, Pool-Zobel et al teach that lignan such as enterolactone reduces oxidized bases at high, non-physiological concentrations but had no effects on oxidative stress (See page 1251, column 2, last paragraph, Fig 4 and 5, in particular). Just like the instant application, Pool-Zobel et al does not teach how to extrapolate in vitro exerperiment to in vivo method of inhibiting overactivity of phagocytes or lymphocytes in all dividuals. It is precisely the point of the Examiner trying to make, that is, different lignans on different cell types have different effects.

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600